

Remarks

The Amendments to the Claims

Claims 1, 34, and 47 have been amended to incorporate the recitation of claim 15, which is now canceled. Claim 17 has been amended to depend from claim 1.

The amendments introduce no new matter. The amendments present the claims in better form for appeal. The amendments were not presented earlier because Applicants believed their previous response would put the claims in condition for allowance.

The Rejections of Claims 1, 2, 5, 15, 18-20, 31, 34, 35, 47, 77, 79, and 83 Under 35 U.S.C. § 112, first paragraph

Claims 1, 2, 5, 15, 18-20, 31, 34, 35, 47, 77, 79, and 83 stand rejected under 35 U.S.C. § 112, first paragraph, as insufficiently described and as not enabled. Claim 15 is canceled. Applicants respectfully traverse the rejections of claims 1, 2, 5, 18-20, 31, 34, 35, 47, 77, 79, and 83.

Written Description

The statutory authority for the written description requirement is 35 U.S.C. § 112, first paragraph, which states:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Compliance with the written description requirement of 35 U.S.C. § 112, first paragraph requires sufficient information in the original disclosure to convince a skilled worker that the inventor possessed the invention at the time of filing. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-

64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). The written description requirement for a claimed genus may be satisfied through description of a representative number of species sufficient to show that the applicant was in possession of the claimed genus. M.P.E.P. § 2163. What constitutes a representative number is an inverse function of the skill and knowledge in the art.

Satisfactory disclosure of a representative number of species exists where the skilled artisan would recognize the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For example, the Federal Circuit has held that claims to a broad genus of known biological materials – cells – rather than new or unknown genetic materials, were adequately described because the claim terms “vertebrate cells” and “mammalian cells” conveyed to the ordinarily skilled artisan adequate information to visualize or recognize the identity of the members of the genus. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1332 (Fed. Cir. 2003). The court further held the disclosed production of erythropoietin in just two species of the disclosed genus of cells adequately supported the claimed production of the polypeptide in the full genus of cells. *Id.*

In the present case, the Patent Office asserts that the specification is deficient in showing that truncation mutants of mammalian PMS2 genes other than human PMS2-134 mutants would cause hypermutability in plant cells. Office Action dated February 12, 2003 at page 6. The written description requirement, however, does not require a demonstration that all dominant negative alleles of mammalian PMS2 proteins encompassed by the claims cause hypermutability in plant cells. Rather, the written description requirement can be fulfilled by a disclosure of

functional characteristics coupled with a known or disclosed correlation between function and structure. 66 Fed. Reg. 1099, 1106 (January 5, 2001). The specification meets this standard.

The claims are directed to methods employing and compositions comprising known biological materials – *i.e.*, mammalian PMS2 genes – rather than new genetic materials. Indeed, the Patent Office acknowledges that PMS2 nucleotide sequences of at least two mammalian species were known at the time of the invention. Office Action dated December 2, 2003 at page 3. Moreover, mammalian PMS2 nucleotide sequences exhibit strong homology, as demonstrated by the BLAST sequence alignment between the human and mouse PMS2 sequences already of record. This evidences the strong conservation of PMS2 genes among widely disparate mammalian species. Thus, the ordinarily skilled artisan would readily recognize the identity of the members of the genus of mammalian PMS2 genes.

Moreover, Applicants have demonstrated that dominant negative alleles of human and plant PMS2 mismatch repair genes having a truncation mutation exert a dominant negative effect upon expression in plant cells to yield a hypermutable phenotype. Specification at Example 3. In view of the strong homology between PMS2 genes and the demonstrated function in plant cells of PMS2 alleles bearing truncation mutations from two widely disparate species, Applicants have disclosed functional characteristics (hypermutability) coupled with a correlation between that function and structure (truncated mammalian PMS2 genes) sufficient to support the genus of mammalian *PMS2* alleles comprising a truncation mutation.

The Patent Office cites Pang *et al.*, *Mol. Cell. Biol.*, 17(8):4465-73, 1997, to support the alleged lack of correlation between structure of mammalian PMS2 mismatch repair proteins having a truncation mutation and a dominant negative effect. Office Action dated December 12, 2003 at pages 3-4. Applicants assert, however, that in view of the substantial guidance presented

in the specification for identifying PMS2 truncation mutants exhibiting a dominant negative mismatch repair phenotype upon expression in cells (Examples 2 and 3; see below), the skilled worker would readily envisage the truncation mutants of mammalian PMS2 genes within the scope of the claims. Thus, the skilled worker would understand that Applicants possessed the claimed invention at the time of filing.

Applicants respectfully request withdrawal of the rejection.

Enablement

Claims 1, 2, 5, 15, 18-20, 31, 34, 35, 47, 77, 79, and 83 are rejected as not enabled. Applicants have amended claim 1 to incorporate the limitation of claim 15 and have canceled claim 15. To the extent the rejection applies to the claims as amended, Applicants disagree with the rejection.

The legal test for whether a disclosure provides adequate enablement for a generic claim is that “the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art.” *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added). The requirement that the patent holder enable the “full scope” of the claimed invention has never been interpreted to require the enablement of every embodiment within the scope of the claims. *See, e.g., In re Wright*, 999 F.2d 1557, 1563, 27 U.S.P.Q.2d (BNA) 1510, 1515 (Fed. Cir. 1993); M.P.E.P. § 2164.03.

The Office Action asserts that the specification is not enabling for methods of generating hypermutable plant cells using any dominant negative allele of any mammalian PMS2 gene or the cells or plants produced by such methods. Office Action at page 5. To advance prosecution, independent claims 1, 37, and 47 have been amended to recite that the dominant negative allele

comprises a truncation mutation. To evaluate the scope of enablement the specification provides for the amended claims, the proper standard is whether any experimentation that the skilled worker may need to practice the claimed invention is undue or unreasonable. *In re Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2d (BNA) at 1404 (Fed. Cir. 1988). Whether a claim is enabled is a question of law based on underlying factual findings. *Wands*, 858 F.2d at 735, 8 U.S.P.Q.2d (BNA) at 1402. The following facts indicate that the specification enables those skilled in the art to identify the recited dominant negative alleles without undue experimentation.

First, the specification teaches that PMS2 homologs from widely disparate species, including *Arabidopsis thaliana* and human, share a high degree of homology. See Figures 5-7.

Second, the high degree of homology between various species translates to conserved function. Indeed, the specification teaches that expression of truncated human and plant PMS2 genes induces the same phenotype. Specification at page 17, lines 3-6.

Third, the specification teaches methods for isolating PMS2 mismatch repair genes in plant species by screening *Arabidopsis thaliana* RNA with degenerate primers derived by aligning *E. coli*, yeast, mouse, and human PMS2 genes followed by screening of an *A. thaliana* cDNA library with plant-specific primers. See Example 1.

Fourth, the specification teaches identification of dominant negative alleles of the plant PMS2 gene bearing a truncation mutation by analyzing the ability of the truncation mutant to generate hypermutability in a test system such as bacterial or mammalian cells. See Example 2.

These teachings in the specification are sufficient to permit one of skill in the art to identify dominant negative alleles of a mammalian *PMS2* gene which comprise a truncation mutation. In view of the high degree of homology shared between mammalian *PMS2* genes, including human and mouse *PMS2* genes, and the conserved function of *PMS2* genes among

species as disparate as humans and plants, one of skill in the art would expect truncated mammalian *PMS2* genes of various mammalian species to exhibit a dominant negative effect in plant cells. For a claimed genus, representative examples together with a statement applicable to the genus as a whole are sufficient to establish enablement if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation. M.P.E.P. § 2164.02.

The Patent Office has advanced no valid reason why a person skilled in the art would not expect truncated *PMS2* genes of mammalian species other than humans to exhibit a dominant negative effect in plant cells. The Patent Office relies on Chang *et al.*, *Genome Research*, 11(7):1145-46, 2001, to support its assertion that the state of the art at the time of filing was unpredictable. Applicants respectfully assert that Chang has no bearing on the enablement of the present claims.

Chang does not teach that mutation of a *PMS2* gene does not result in a mutator phenotype, but rather speculates that the loss of *PMS2* activity may result in a weaker mutator phenotype than occurs with loss of *MSH2* or *MLH1*. Chang also asserts that the strong mutator phenotype associated with loss of *MSH2* or *MLH1* activity would be less capable of overcoming the hazardous effects of the accumulation of deleterious mutations. In other words, the phenotype would be lethal. See Chang, Figure 1. Notably, Chang provides no data to support the assertions made therein. Moreover, the specification teaches that expression of dominant negative alleles of truncation mutants of *PMS2* yields loss of mismatch repair activity, thereby resulting in hypermutability, not lethality. This is not inconsistent with Chang's model of survival advantage of the "weaker" mutator phenotype.

The Patent Office also relies on Pang to support its assertion that one of skill in the art could not predict which PMS2 gene truncation mutants would produce a dominant negative effect. Pang describes one truncated PMS2 protein whose expression did not yield a dominant negative mismatch repair phenotype in yeast. But Pang also describes several truncated PMS2 proteins whose expression does result in a dominant negative mismatch repair phenotype. Pang, page 4471. Pang's disclosure in fact weighs in favor of enablement, because it demonstrates that it does not require undue experimentation to identify *PMS2* truncations that confer a dominant negative mismatch repair phenotype in a cell.

Enablement does not require 100% success. *Wands*, 8 U.S.P.Q.2d at 1406. Enablement requires only that the specification teaches one skilled in the art how to make and use the invention without undue experimentation. The specification satisfies this requirement. In view of the guidance and working examples in the specification, the high level of skill in the art, and the predictability of the invention, it would not require undue experimentation to practice the invention of the pending claims.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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